06-07-00 A

PATENT

Docket No. 16230-4923

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this June 6, 2000 in an envelope as "Express Mail Post Office to Addressee" Mail Label Number EL470435773US addressed to: Box Patent Application, Assistant Commissioner of Patents, Washington, D.C. 20231.

Cathy Marino
(Type name of person mailing paper)

Cathy Marino
(Signature of person mailing paper)

NOTE: Each paper or fee referred to as enclosed herein has the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 CFR 1.10(b).

Box Patent Application
Assistant Commissioner of Patents
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

Inventor(s): Luthra, Ajay Kumar; Sandhu, Shivpal Singh

For : NON-THROMBOGENIC AND ANTI-THROMBOGENIC POLYMERS

Enclosed are:

1. Benefit of Prior U.S. Application (35 USC 120)

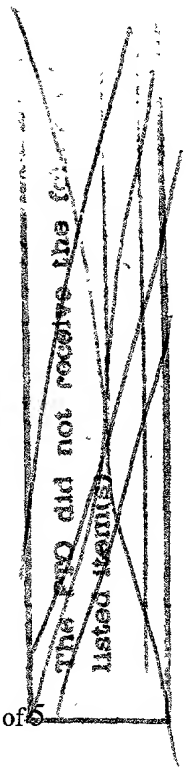
X The new application being transmitted claims the benefit of a prior U.S. application and enclosed is added page for new application transmittal where benefit of a prior U.S. application claimed.

2. The Papers Required For Filing Under 37 CFR 1.53:

26 Pages of Specification
1 Pages of Abstract
4 Pages of Claims and 7 pages of a Preliminary Amendment dated October 29, 1998 with Claims 22-46, and Abstract.
0 Sheets of Drawing

X formal ___ informal

In addition to the above papers there is also attached:
1 Pages of Amendments
X Return Receipt Postcard
___ Information Disclosure Statement with ___ copies of references.



3. Declaration or oath

__X__ Enclosed __3__ pages
- ___ Newly executed (original or copy)
- __X__ Copy from a prior application (continuation/divisional with page 5 of 5 completed)
- ____ Deletion of Inventor(s) (signed statement attached deleting inventor(s) of prior application)

____ Not enclosed

4. Inventorship Statement

The inventorship for all the claims in this application are:

__X__ the same

OR

____ are not the same and an explanation, including the ownership of the various claims at the time the last claimed invention was made, is submitted.

5. Language

__X__ English ___ Non-English

A verified English translation of the

[check applicable item(s)]

- ____ specification and claims
- ____ declaration

is attached.

6. Assignment

____ An assignment of the invention to

- ____ is filed under separate cover sheet
- ____ was filed in the prior application
- ____ will follow

7. Certified Copy

(Country) (Application No.) (Filed)

from which priority is claimed

- ____ is attached
- ____ will follow

8. Fee Calculation

CLAIMS AS FILED

	Number Filed	Provided with Basic Fee	Number Extra	Rate	Basic Fee $690
Total Claims	2	20	0	X $18.00	$ .00
Independent Claims	1	3	0	X $78.00	$ .00
Multiple Dependent Claim(s), if any	0	0	0	X $260.00	$ .00

_X_ Amendment canceling Claims 1-42 and 45-106 prior to the filing of the fees is enclosed.

____ Amendment deleting multiple dependencies enclosed

____ Fee for extra claims is not being paid at this time

Filing Fee Calculation $ 690.00

9. Small Entity Statement

____ verified statement that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is attached.

Filing Fee Calculation (50% of above) $_____

10. Fee Payment Being Made At This Time

_X_ Enclosed

_X_ basic filing fee $ 690.00

Total fees enclosed $ 690.00

11. Method of Payment of Fees

_X_ check in the amount of $ 690.00

12. Authorization to Charge Additional Fees

_X_ The Commissioner is hereby authorized to charge the following additional fees which may be required to Account No. 18-1829;

_X_ 37 CFR 1.16 (filing fees and presentation of extra claims)

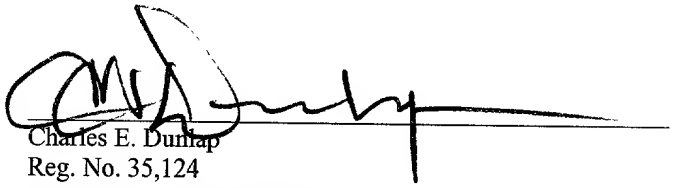
_X_ 37 CFR 1.17 (application processing fees)

___ 37 CFR 1.18 (issue fee at or before Mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b).

13. Instructions As To Overpayment

_X_ credit Account No. 18-1829

14. Correspondence Address



Charles E. Dunlap
Reg. No. 35,124
HOWELL & HAFERKAMP, L.C.
7733 Forsyth Boulevard
Suite 1400
St. Louis, Missouri 63105
(314) 727-5188

ADDED PAGE FOR NEW APPLICATION WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED

15. Benefits of Prior U.S. Application

This application is a

____ continuation

____ continuation-in-part

__X__ divisional

of prior U.S. application Serial No. 09/171,948 filed October 29, 1998 which claims priority to

International Application PCT/GB97/01173 filed April 30, 1997

__X__ Incorporation by Reference
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under item 3., is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

16. Maintenance of Copendency of Prior Application

____ A petition, fee and response has been filed to extend the term in the pending prior application until

17. Conditional Petition for Extension of Time in Parent Application

____ A conditional petition for extension of time is being filed in the pending parent application.

18. Relate Back – 35 U.S.C. 120

__X__ Amend the specification by inserting before the first line the sentence:

This is a

____ continuation
____ continuation-in-part
__X__ divisional
____ provisional

of copending application

__X__ Serial number 09/171,948 ; filed on October 29, 1998, which was a § 371 of
__X__ PCT International Application PCT/GB97/01173 ; filed on April 30, 1997.

19. Abandonment of Prior Application (if applicable)

___ Please abandon the prior application at a time while the prior application is pending or when the petition for extension of time in that application is granted and when this application is granted a filing date so as to make this application copending with said prior application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this correspondence and the documents referred to as enclosed therein are being deposited with the United States Postal Service on June 16, 2000 in an envelope as 'Express Mail Post Office To Addressee' Mailing Label Number EL470435773US addressed to: BOX PATENT APPLICATION, Assistant Commissioner for Patents, Washington, D.C. 20231.

Cathy Marino
Type or Print Name

Cathy Marino
Signature

In re application of: Luthra et al. :
Docket No.: 16230-4923 :
Filed: :
For: NON-THROMBOGENIC AND :
ANTI-THROBOGENIC POLYMERS :

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

This paper is submitted as a preliminary amendment in the above-identified case, which is a divisional of copending Serial No. 09/171,948, which in turn is a national stage filing under 35 U.S.C. §371 of PCT/GB97/01173. It is respectfully requested that Claims 1-42 and 45-106 be cancelled without prejudice or disclaimer.

Respectfully submitted,

Charles E. Dunlap
Reg. No. 35,124
Howell & Haferkamp, L.C.
7733 Forsyth Boulevard, Suite 1400
St. Louis, Missouri 63105
(314) 727-5188

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

St. Louis, Missouri
October 29, 1998

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this correspondence and the documents referred to as enclosed therein are being deposited with the United States Postal Service on Oct 29, 1998 in an envelope as 'Express Mail Post Office To Addressee' Mailing Label Number EL175699005US addressed to: Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231.

Mary L. Ogolin
Name

Mary L. Ogolin
Signature

In re application of:
LUTHRA, A.K., and S. S. SANDHU

Serial No.:

Filed:

For: NON-THROMBOGENIC AND ANI-THROMBOGENIC POLYMERS

Examiner

Group Art Unit

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

This Preliminary Amendment is filed concurrently with the filing of the patent application identified above for entrance into the national phase in the United States based on International Application No. PCT/GB97/01173, filed April 30, 1997. It is respectfully requested that the application be amended as requested below and that the application be examined on the merits.

IN THE ABSTRACT:

An ABSTRACT OF THE DISCLOSURE is provided on a separate sheet as provided in 37 CFR §1.72(b). It is respectfully requested that the ABSTRACT be entered into the case.

IN THE SPECIFICATION:

Please amend the specification as follows:

The following typographical error should be corrected:

In formula number 3, page 7, the term "R_1" should be replaced with the term --- R_4 ---;

IN THE CLAIMS:

Please amend the claims as follows:

Please cancel claims 1 - 21, without prejudice.

Please add new claims 22 - 46 as shown below:

-- 22. Copolymers comprising a polymer backbone having pendant groups, which comprise monomer units of at least three different classes selected from:

(a) monomers having sulphate groups,

(b) monomers having sulphonate groups,

(c) monomers having sulphamate groups, and

(d) monomers having polyoxyalkylene ether groups.

23. Copolymers comprising a polymer backbone having pendant groups, which comprise monomer units of at least three different classes selected from:

(a) monomers having sulphate groups,

(b) monomers having sulphonate groups,

(c) monomers having sulphamate groups,

(d) monomers having polyoxyalkylene ether groups, and

(e) monomers having zwitterionic groups.

24. Copolymers according to claim 22 which contain additional monomer units derived from acrolein.

25. Copolymers according to claim 23 which contain additional monomer units derived from acrolein.

26. Copolymers according to any one of claims 22, 23, 24, or 25 wherein said monomer units in classes (a), (b) or (c) have the formula:

$$CH_2=CR_1\text{-}C(=O)\text{-}Z_1\text{-}R_2\text{-}Y_1\text{-}X_1$$

where

R_1 is selected from H and CH_3;

R_2 is selected from linear or branched alkylene groups of 2 - 10 carbon atoms, phenylene, phenyl alkylene with 1 - 10 carbon atoms in the alkylene structure, and the polyalkylene group $(CH_2\text{-}CHR_1\text{-}O)_n$ where R_1 is selected from H and CH_3 and n is from 2 to 50;

Z_1 is selected from oxygen (-O-) to give an ester linkage and secondary amine (-NH-) to give an amide linkage;

Y_1 is (-O-) or (-NH-) or is absent; and

X_1 is a sulphonate anionic group ($-SO_3^-$); balanced by a physiologically-acceptable cation.

27. Copolymers according to any one of claims 22, 23, 24 or 25 wherein said monomer units in classes (a), (b) or (c) have the formula:

$CH_2=CR_1\text{-}R_2\text{-}Y_1\text{-}X_1$

where

R_1 is selected from H and CH_3;

R_2 is selected from linear or branched alkylene groups of 2 - 10 carbon atoms, phenylene, phenyl alkylene with 1 - 10 carbon atoms in the alkylene structure, and the polyoxyalkylene group $(CH_2\text{-}CHR_1\text{-}O)_n$ where R_1 is selected from H and CH_3 and n is from 2 to 50;

Z_1 is selected from oxygen (-O-) to give an ester linkage and secondary amine (-NH-) to give an amide linkage;

Y_1 is (-O-) or (-NH-) or is absent; and

X_1 is a sulphonate anionic group ($-SO_3^-$); balanced by a physiologically-acceptable cation.

28. Copolymers according to claim 26 wherein the monomer units containing sulphate groups are selected from salts of 2-sulphatoethyl methacrylate, 2-sulphatoethyl acrylate, 3-sulphatopropyl methacrylate, 3-sulphatopropyl acrylate, 4-sulphatobutyl methacrylate, 4-sulphatobutyl acrylate, 2-sulphatoethyl methacrylamide, 2-sulphatoethyl acrylamide, 3-sulphatopropyl methacrylamide, 3-sulphatopropyl acrylamide, 4-sulphatobutyl methacrylamide, 4-sulphatobutyl acrylamide, sulphato polyoxyalkylene methacrylate, and sulphato polyoxyalkylene acrylate.

29. Copolymers according to claim 27 wherein the monomer units containing sulphate groups are selected from salts of allyl sulphate, methyl allyl sulphate, 3-buten-1-sulphate, 3-buten-2-sulphate, 2-methyl-2-propane-1-sulphate, 2-methyl-3-buten-1-sulphate and 3-methyl-3-buten-1-sulphate.

30. Copolymers according to claim 26 wherein the monomer units containing sulphonate groups are selected from salts of 2-sulphoethyl methacrylate, 2-sulphoethyl acrylate, 3-sulphopropyl methacrylate, 3-sulphopropyl acrylate, 2-acrylamide-methylpropanesulphonate, 3-sulphopropyl ethoxy methacrylate, 3-sulphopropyl ethoxy acrylate, 3-sulphopropyl polyoxyalkylene methacrylate, and 3-sulphopropyl polyoxyalkylene acrylate.

31. Copolymers according to claim 27 wherein the monomer units containing sulphonate groups are selected from salts of vinyl sulphonate, allyl sulphonate, methyl allyl sulphonate and p-styrene sulphonate.

32. Copolymers according to claim 26 wherein the monomer units containing sulphamate groups are selected from salts of 2-sulphamatoethyl methacrylate, 2-sulphamatoethyl acrylate, 3-sulphamatopropyl methacrylate, 3-sulphamatopropyl acrylate, 4-sulphamatobutyl methacrylate, 4-sulphamatobutyl acrylate, 2-sulphamatoethyl methacrylamide, 2-sulphamatoethyl acrylamide, 3-sulphamatopropyl methacrylamide, 3-sulphamatopropyl acrylamide, 4-sulphamatobutyl methacrylamide, 4-sulphamatobutyl acrylamide, sulphamato polyoxyalkylene methacrylate and sulphamato polyoxyalkylene acrylate.

33. Copolymers according to claim 27 wherein the monomer units containing sulphamate groups are selected from salts of allyl sulphamate and methyl allyl sulphamate.

34. Copolymers according to any one of claims 22, 23, 24 or 25 wherein said monomer units in class (d) have the formula:

$$CH_2=CR_3\text{-}C(=O)\text{-}O\text{-}(CH_2\text{-}CHR_4\text{-}O)_n\text{-}CH_3$$

where R_3 and R_4, which may be the same or different, are each selected from H and CH_3; R_7 is selected from H and alkyl with from 1 to 5 carbon atoms; and n is from 2 to 50.

35. Copolymers according to claim 22 or 23 wherein said polymers additionally contain additional monomer units derived from monomer units having heparin linked to a polymerizable moiety having a carbon-carbon double bond.

36. Copolymers according to claim 35 wherein the heparin monomer units comprise polymerizable groups selected from vinyl, allyl, methallyl, acrylate and methacrylate groups.

37. Copolymers according to claim 32 wherein the heparin monomer units have the formula:

$$CH_2=CR_5\text{-}C(=O)\text{-}O\text{-}CH_2\text{-}CHR_6\text{-}(O\text{-}CH_2\text{-}CHR_6\text{-})_n\text{-}O\text{-}C(=O)\text{-Heparin}$$

or

$$CH_2=CR_5\text{-}C(=O)\text{-}O\text{-}CH_2\text{-}CHR_6\text{-}(O\text{-}CH_2\text{-}CHR_6\text{-})_n\text{-}O\text{-}C(=O)\text{-}O\text{-Heparin}$$

where R_5 and R_6, which may be the same or different, are each selected from H and CH_3; and n is from 0 to 49.

38. Copolymers according to claim 22 or 23 wherein said polymers additionally contain additional monomer units derived from monomer units having hiruden, warfarin or hyaluronic acid linked to a polymerizable moiety having a carbon-carbon double bond.

39. A medical device having a coating of a polymer according to claim 22 or 23.

40. A method of forming a coating of a polymer according to any one of claim 22 or 23 on a medical device, which comprises forming an ungelled partial polymer by reacting a solution of an amine polymer with a crosslinking agent, activating the medical device by solution coating with said partial polymer, and depositing the polymer on the resulting activated medical device.

41. A method according to claim 40 wherein the amine polymer is polyethylene imine.

42. A method according to claim 40 wherein the crosslinking agent is an aliphatic monoisocyanate or diisocyanate.

43. A heparin monomer having the formula:

$$CH_2=CR_5\text{-}C(=O)\text{-}O\text{-}CH_2\text{-}CHR_6\text{-}(O\text{-}CH_2\text{-}CHR_6\text{-})_n\text{-}O\text{-}C(=O)\text{-Heparin}$$

or

$$CH_2=CR_5\text{-}C(=O)\text{-}O\text{-}CH_2\text{-}CHR_6\text{-}(O\text{-}CH_2\text{-}CHR_6\text{-})_n\text{-}O\text{-}C(=O)\text{-}O\text{-Heparin}$$

where R_5 and R_6, which may be the same or different, are each selected from H and CH_3; and n is from 0 to 49.

44. A method of forming a heparin monomer according to claim 43, wherein a hydroxyl terminated compound of the formula:

$$CH_2=CR_5\text{-}C(=O)\text{-}O\text{-}CH_2\text{-}CHR_6\text{-}(O\text{-}CH_2\text{-}CHR_6\text{-})_n\text{-OH}$$

is reacted with carbonyldiimidazole to form an activated imidazoyl carbonate of the formula:

$$CH_2=CR_5\text{-}C(=O)\text{-}O\text{-}CH_2\text{-}CHR_6\text{-}(O\text{-}CH_2\text{-}CHR_6\text{-})_n\text{-}O\text{-}C(=O)\text{-}Im$$

where R_5 and R_6, which may be the same or different, are each selected from H and CH_3; and n is from 0 to 49, and the activated inidazoyl carbonate is coupled with heparin at a basic pH.

45. A coating material comprising a copolymer according to claim 22 or claim 23.

46. A coating material according to claim 45 adapted for use on a surface of a medical device. ---

REMARKS

The specification has been amended to correct a typographical error in formula 3, page 7. Support for the correct terminology for the formula can be found at least in original claim 8 and in the description of formula 3, as it appears immediately after the formula on page 7 of the specification.

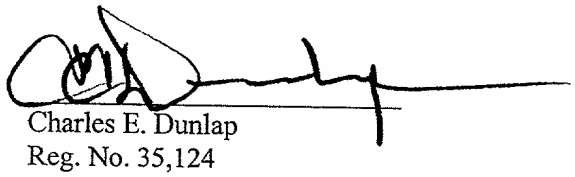
An abstract of the disclosure has been enclosed herewith on a separate sheet as provided in 37 CFR §1.72(b). It is respectfully requested that such abstract be entered into the case.

Claims 1 - 21 have been cancelled without prejudice. New claims 22 - 46 have been added. The new claims find support in the cancelled claims and in the specification and have been redrafted to reduce the number of multiple dependent claims and to more clearly describe the claimed invention. No new matter has been added.

Request for Examination:

It is believed that this application is now in condition for examination and allowance and such actions are respectfully requested. If the Examiner finds, for any reason, one or all of the claims not to be allowable, it is requested that a telephone call be made to the undersigned at the number given below prior to the issuance of any final rejection so that any remaining issues can be resolved.

Respectfully submitted,



Charles E. Dunlap
Reg. No. 35,124
Howell & Haferkamp, L.C.
7733 Forsyth Boulevard, Suite 1400
St. Louis, Missouri 63105
(314) 727-5188

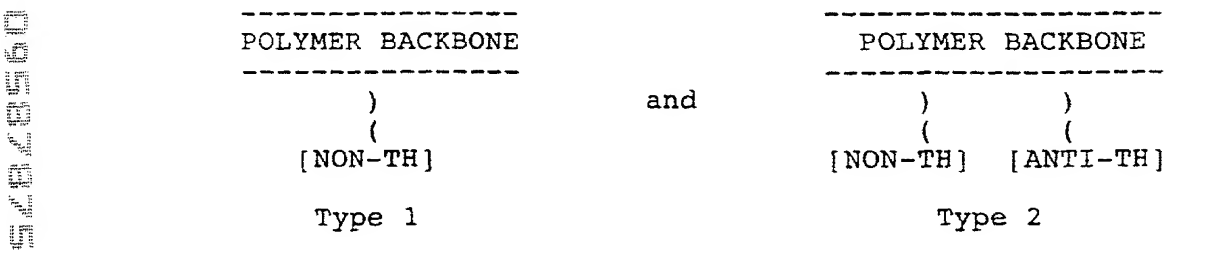
ABSTRACT OF THE DISCLOSURE

Polymers having non-thrombogenic properties can be prepared by copolymerizing monomers of at least three classes selected from (a) monomers having sulphate groups, (b) monomers having sulphonate groups, (c) monomers having sulphamate groups, (d) monomers having polyoxyalkylene ether groups, and (e) monomers having zwitterionic groups. The polymers can additionally be provided with anti-thrombogenic properties by including an additional comonomer having a pendant heparin (or hirudin, warfarin or hyaluronic acid) group. The polymers can be used as coating materials for medical devices, such as tubing or connectors, in order to provide them with non-thrombogenic, and optionally anti-thrombogenic, properties.

NON-THROMBOGENIC AND ANTI-THROMBOGENIC POLYMERS

SUMMARY OF INVENTION

This invention relates to the synthesis of polymers which contain non-thrombogenic (NON-TH) as well as anti-thrombogenic (ANTI-TH) properties. Such polymers can be conveniently represented as follows:



In schematic diagrams of this kind, as used herein, the designated side chains or groups can occur in any order and in any relative proportions along the polymer backbone.

In polymers of Type 1 the non-thrombogenic (NON-TH) component may consist of non-ionic hydrophilic domains, ionic domains, zwitterionic domains or combinations of such domains. In novel Type 1 polymers in accordance with the invention, such non-thrombogenic components may be selected from, but are not limited to, polymerisable sulphonates, polymerisable sulphates, polymerisable N-sulphates (also known as sulphamates), polymerisable zwitterionic compounds, and polymerisable polyethylene glycols. When we synthesised polymers of Type 1, without the anti-thrombogenic component, and coated various medical devices, we found blood cell and protein deposition reduced by greater than 90%. Greatly reduced (>95%) activation

of white cells, platelets and complement was observed. This type of synthetic polymer can be described as a non-thrombogenic polymer.

The non-thrombogenic Type 1 polymer, as described, was synthesised with polymerisable Heparin to give a Type 2 polymer. Surprisingly, the activity of the heparin was retained in the Type 2 polymer and such polymers, when coated on to medical devices, had the additional property of reducing the thrombin-antithrombin complex concentration. This inclusion of heparin into the non-thrombogenic polymer gave a new polymer which additionally exhibited anti-thrombogenic properties.

Another aspect of this invention is the process by which the non-thrombogenic and anti-thrombogenic polymers are coated onto medical devices.

BACKGROUND TO THE INVENTION

There is a growing interest in the use of artificial materials in clinical practice where these materials are in continuous contact with blood. Medical devices made from these materials are required to perform in the harsh biological environment in a specific application, for a specific duration without stimulating a biological response which may prove to be detrimental. Hence, such devices are required to be accepted by the biological environment for a specific application and duration, ie need to be bioacceptable. Improvements in bioacceptability are highly desirable for medical devices manufactured from artificial materials. Such materials commonly include polyvinyl chloride, polyethylene, polypropylene, polyurethanes, polycarbonates, stainless steel, silicones and the like. The biological response to blood contact with an artificial surface can be regarded in terms of

different contributions from protein, platelet and blood cell deposition, together with platelet and blood activation leading to thrombus formation.

Many investigations have been carried out to prevent an artificial surface from provoking thrombus formation, ie to form a bioacceptable surface. Such investigations include the use of polymers which are natural, hydrophilic, hydrophobic, zwitterionic and charged (anionic and cationic). These types of polymers are non-thrombogenic, have had limited success and therefore application. Surface modification of an artificial material by heparin (ie formation of an anti-thrombogenic surface) has also proved to be intractable. Although clot formation has been reduced, platelet activation and blood cell activation are however still prevalent. Similarly, a particular artificial surface may be resistant to protein, platelet and blood cell deposition but may still activate blood constituents.

Each surface, whether non-thrombogenic or anti-thrombogenic, has its own profile of desirable bioacceptable properties, but no particular material possesses the full spectrum of the desired properties.

Additional disadvantages of some of the known approaches are (i) the procedures used to produce these materials are complex, (ii) the methods of applying these materials to the medical device are elaborate, and (iii) these processes utilise reagents which are highly toxic, even in minute quantities.

In a new approach to the problem of finding suitable bioacceptable materials, we have synthesised a novel non-thrombogenic polymer, and have also modified non-thrombogenic polymers by incorporating a polymerisable anti-thrombogenic compound, exemplified by polymerisable heparin. It was found that heparin activity was maintained,

while the non-thrombogenity of the polymer component was prevalent. Other known biologically active anti-thrombogenic compounds include hirudin, warfarin and hyaluronic acid, and can be used in the same manner as the polymerisable heparin.

THE INVENTION

One embodiment of the present invention provides polymers comprising a polymer backbone having pendant groups, obtainable by polymerising monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

(a) monomers having sulphate groups
(b) monomers having sulphonate groups
(c) monomers having sulphamate groups, and
(d) monomers having polyoxyalkylene ether groups.

Another embodiment of the present invention provides polymers comprising a polymer backbone having pendant groups, obtainable by polymerising monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

(a) monomers having sulphate groups
(b) monomers having sulphonate groups
(c) monomers having sulphamate groups
(d) monomers having polyoxyalkylene ether groups, and
(e) monomers having zwitterionic groups.

A further embodiment of the present invention provides a method of forming a coating of a polymer as described above on a medical device by forming an ungelled partial polymer by reacting a solution of an amine polymer with a crosslinking agent, activating the medical device by solution coating with said partial polymer, and depositing the polymer on the resulting activated medical device.

The present invention also provides a coating material comprising a polymer as described above.

Without wishing to be bound by any theory or explanation of the invention, it appears that non-thrombogenic surfaces have an important impact on the first event of contact of blood with an artificial surface. This event occurs almost instantaneously and consists of protein adsorption. Subsequent events are largely determined by interactions of blood with the adsorbed protein. The nature of the artificial surface determines the manner and extent of protein attachment.

For hydrophobic surfaces, attachment occurs by hydrophobic interactions with the protein, which causes conformational change of the adsorbed protein, exposing sites for protein interaction resulting in further protein adsorption. The next sequence of events has a pronounced influence in promoting platelet adsorption/activation and white cell adsorption/ activation. The consequence of these events is the formation of thrombus.

Protein adsorption on hydrophilic surfaces is more readily and rapidly reversible than on hydrophobic surfaces. The extent of reversibility is determined by the nature of the chemical bond in the equilibrium state. At high states of reversibility, protein adsorption is not prevalent and consequently platelet and white cell adsorption/activation is prevented. Therefore, thrombus formation is averted.

This type of hydrophilic surface is regarded as being non-thrombogenic and in this respect we have found a new artificial hydrophilic polymer with at least three different types of hydrophilic groups which include, but are not restricted to, sulphonate, sulphate, N-sulphate (sulphamate) or zwitterionic groups, and polyethylene glycol or glycol ether units in the same polymer backbone.

In one embodiment of the present invention the non-thrombogenic polymer is obtainable by radical polymerisation, preferably of monomers having reactive carbon-carbon double bonds to form the polymer backbone and said monomer constituents containing, but not limited to, sulphonates, sulphates, N-sulphates (sulphamates), zwitterions, and polyethylene glycol units, these monomer constituents being contained in the same polymer composition. Such monomers may be separated into three groups.

The first group is based on monomers derived from acrylates or methacrylates of sulphonates, sulphates and N-sulphates:

1) $CH_2=CR_1-C(=O)-Z_1-R_2-Y_1-X_1$

Where R_1 is H or CH_3;
R_2 is a linear or branched alkylene of 2-10 carbon atoms, phenylene, phenyl alkylene with 1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure $[CH_2-CHR_1-O]_n$ where R_1 is H or CH_3 and n is from 2 to 50;
Z_1 is oxygen (-O-) to give an ester linkage or secondary amine (-NH-) to give an amide linkage;
Y_1 is (-O-) or (-NH-) or is absent; and
X_1 is sulphonate ($-SO_3^-$)
together with an acceptable balancing cation.

The second group is based on monomers derived from vinyl, allyl or methyl allyl, of sulphonates, sulphates and N-sulphates:

2) $CH_2=CR_1-R_2-Y_1-X_1$

Where R_1 is H or CH_3;
R_2 is a linear or branched alkylene of 1-10 carbon atoms, phenylene, phenyl alkylene with

1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure $[CH_2-CHR_1-O]_n$ where
R_1 is H or CH_3 and n is from 2 to 50;
Y_1 is (-O-) or (-NH-) or is absent; and
X_1 is sulphonate ($-SO_3^-$)
together with an acceptable balancing cation.

In both groups of monomers (1) and (2),
when Y_1 is (-O-), the monomer terminates in a sulphate group;
Y_1 is (-NH-), the monomer terminates in a N-sulphate group;
R_2 and Y_1 are not present, the monomer terminates in a sulphonate group;
R_2 is polyoxyalkylene and Y_1 is not present, the monomer terminates in a sulphate group.

The third group of monomers is derived from acrylates or methacrylates of polyoxyalkylene glycols or glycol ethers:

3) $CH_2=CR_3-C(=O)-O-[CH_2-CHR_1-O]_n-R_7$

Where R_3 and R_4, which may be the same or different, are each H or CH_3, R_7 is H or alkyl with 1 to 5 carbon atoms, eg methyl, and
n is an integer from 2 to 50.

Monomer examples incorporating sulphonate groups include, but are not restricted to, salts of:
2-sulphoethyl methacrylate, 2-sulphoethyl acrylate, 3-sulphopropyl methacrylate, 3-sulphopropyl acrylate, vinyl sulphonate, allyl sulphonate, methyl allyl sulphonate, *p*-styrene sulphonate, 2-acrylamido-methylpropanesulphonate,

3-sulphopropyl ethoxy methacrylate, 3-sulphopropyl ethoxy acrylate, 3-sulphopropyl polyoxyalkylene methacrylate, 3-sulphopropyl polyoxyalkylene acrylate.

Similarly, examples of monomers terminating in sulphate groups include, and are not confined to, salts of:
2-sulphatoethyl methacrylate, 2-sulphatoethyl acrylate, 3-sulphatopropyl methacrylate, 3-sulphatopropyl acrylate, 4-sulphatobutyl methacrylate, 4-sulphatobutyl acrylate, allyl sulphate, methyl allyl sulphate, 3-buten-1-sulphate, 3-buten-2-sulphate, 2-methyl-2-propane-1-sulphate, 2-methyl-3-buten-1-sulphate, 3-methyl-3-buten-1-sulphate, 2-sulphatoethyl methacrylamide, 2-sulphatoethyl acrylamide, 3-sulphatopropyl methacrylamide, 3-sulphatopropyl acrylamide, 4-sulphatobutyl methacrylamide, 4-sulphatobutyl acrylamide, sulphato polyoxyalkylene methacrylate, sulphato polyoxyalkylene acrylate.

Examples of N-sulphate (sulphamate) containing monomers include, but are not limited to, salts of:
2-sulphamatoethyl methacrylate, 2-sulphamatoethyl acrylate, 3-sulphamatopropyl methacrylate, 3-sulphamatopropyl acrylate, 4-sulphamatobutyl methacrylate, 4-sulphamatobutyl acrylate, allyl sulphamate, methyl allyl sulphamate, 2-sulphamatoethyl methacrylamide, 2-sulphamatoethyl acrylamide, 3-sulphamatopropyl methacrylamide, 3-sulphamatopropyl acrylamide, 4-sulphamatobutyl methacrylamide, 4-sulphamatobutyl acrylamide, sulphamato polyoxyalkylene methacrylate, sulphamato polyoxyalkylene acrylate.

The salts used to form the polymers according to the invention, including those listed above, will have an acceptable, especially physiologically acceptable, balancing cation such as an alkali metal (eg sodium) cation, or an ammonium or substituted ammonium cation. Hydrogen cations usually provide a polymer that is too acidic for the preferred use.

Other examples of non-thrombogenic polymers include those in which zwitterionic monomers may be included in the above formulations. For example, the non-thrombogenic polymers can contain any zwitterionic monomer as an integral part of the polymer backbone. The zwitterionic monomers may also be included in the non-thrombogenic/antithrombogenic polymers. Such zwitterionic monomers include, but are not limited to, 2-(methacryloyloxyethyl)-2'-(trimethylammonium) ethyl phosphate inner salt and dimethyl (2-methacryloylethyl)-[1-(2-sulphopropyl)] ammonium betaine inner salt.

A wide range of monomer compositions can be utilised in the formation of the non-thrombogenic polymer. Such a polymer may contain, and is not limited to, 3 to 4 different monomer constituents. The ter-polymer (3 different monomers) and the tetra-polymer (4 different monomers) are formulated from 3 or 4 respectively of at least one sulphate monomer type, at least one sulphonate monomer type, at least one sulphamate monomer type, and at least one polyoxyalkylene monomer type in the final polymer composition. This polymer composition can accordingly be schematically represented as follows, where the relative frequency and the order of occurrence of each monomer type are variable (being random co-polymers). In each instance anions shown are balanced by acceptable cations, such as those mentioned above.

a) ter-polymer

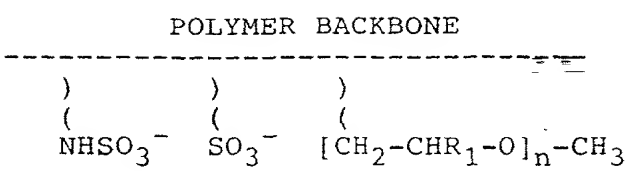
i)

POLYMER BACKBONE		
)	)	)
(	(	(
SO_3^-	SO_4^-	$[CH_2-CHR_1-O]_n-CH_3$

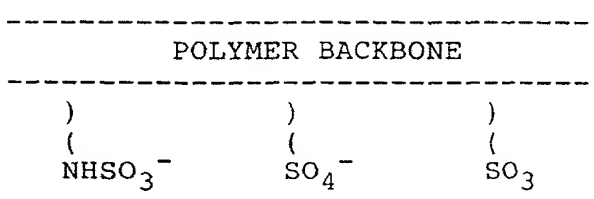
ii)

POLYMER BACKBONE		
)	)	)
(	(	(
$NHSO_3^-$	SO_4^-	$[CH_2-CHR_1-O]_n-CH_3$

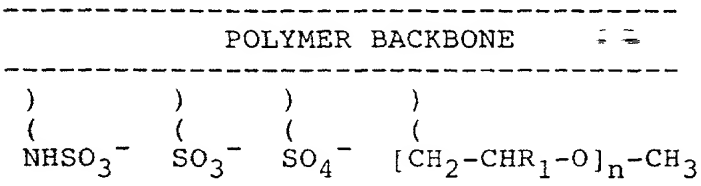
iii)



iv)



b) tetra-polymer



The above co-polymerised monomer compositions are examples of non-thrombogenic (NON-TH) polymers represented above as Type 1.

In another aspect of this invention the non-thrombogenic component is accompanied by a polymerisable anti-thrombogenic component such as polymerisable heparin in the same polymer backbone, and said anti-thrombogenic component in its bioactive form being carried by an integral part of the aforementioned polymer backbone.

Functionalisation of heparin by methacrylation of heparin is known (ACS Symposium Series 77; Carbohydrate Sulphates, 1978). Subsequent known polymerisations with other monomers give rise to anti-thrombogenic polymers only, containing no non-thrombogenic component (of the kind referred to herein).

This aspect of this invention accordingly provides a polymer containing non-thrombogenic and anti-thrombogenic constituents on the same polymer backbone. Preferred non-thrombogenic constituents may comprise sulphate, sulphamate, sulphonate,

zwitterionic and polyoxyalkylene glycol and glycol ether, together with anti-thrombogenic constituents consisting of polymerisable heparin bearing carbon-carbon double bonds. Essentially the carbon-carbon double bond carried by the heparin moiety is polymerisable by a free radical process and may be by way of example vinyl, allyl, methyl allyl, acrylate or methacrylate. Heparin linked to a component containing a polymerisable carbon-carbon double bond is hereafter referred to as heparin monomer. Corresponding monomers in which the heparin is replaced by hirudin, warfarin or hyaluronic acid moieties may be used in like manner.

The favoured heparin monomers are those in which heparin is linked to a polyoxyalkylene methacrylate or polyoxyalkylene acrylate through an ester or carbonate linkage. The ester or carbonate linkage is formed by activating the hydroxyl terminating polyoxyalkylene methacrylate or acrylate with carbonyldiimidazole, forming the activated imidazoyl carbonate, which subsequently is either coupled to carboxylic groups of the heparin molecule to yield an ester linkage or coupled to hydroxyl groups of the heparin molecule to yield a carbonate linkage. This means of attaching the polyoxyalkylene methacrylate or acrylate group to heparin allows polymerisation of the heparin with the desired biological properties. Other coupling techniques as described in WO 91/16932 using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide result in linkages occurring on sulphate groups of the heparin, called a sulphonamide linkage. This coupling procedure results in poor biological properties since these N-sulphate and sulphate groups are important for binding to antithrombin.

Preferred heparin monomers include those of the following formula:

(1) With ester linkage to heparin

$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-Heparin$

(2) With carbonate linkage to heparin

$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-O-Heparin$

In both general formulae, R_5 and R_6, which may be the same or different, are each H or CH_3; and n is an integer from 0 to 49.

Particularly preferred heparin monomers are those derived from polyethylene oxide units, that is to say where R_2 is H.

The heparin monomers (1) and (2), as above, are novel and are other aspects of this invention and may be produced by reacting hydroxyl terminated polyoxyalkylene with carbonyldiimidazole [Im-C(=O)-Im] to form the activated imidazoyl carbonate:

$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-Im$

where R_5, R_6 and n have the meanings given above,

this being followed by the coupling of the activated imidazoyl carbonate to heparin under basic pH conditions using bicarbonate buffer at room temperature.

The heparin monomer is polymerised with the aforementioned monomer of sulphate, sulphamate, sulphonate and polyoxyalkylene, producing a polymer with both non-thrombogenic and anti-thrombogenic properties. This polymer composition may contain 4 to 5 of the different types of monomer constituent. The tetra-polymer (4 different monomer types) and the penta-polymer (5 different monomer types) are so formulated from 3 or 4 respectively of at least one sulphate monomer type, at least one sulphonate monomer type, at least one sulphamate

monomer type, and at least one polyoxyalkylene monomer type, together with at least one heparin monomer type, in the final polymer composition. This polymer composition can accordingly be schematically represented as follows, the relative frequency and the order of occurrence of each monomer type being variable. In each instance the anions shown are balanced by acceptable cations, such as those mentioned above.

a) tetra-polymer i)

POLYMER BACKBONE			
)	)	)	)
(	(	(	(
SO_3^-	SO_4^-	$[CH_2-CHR_1-O]_n-CH_3$	Hep

ii)

POLYMER BACKBONE			
)	)	)	)
(	(	(	(
$NHSO_3^-$	SO_4^-	$[CH_2-CHR_1-O]_n-CH_3$	Hep

iii)

POLYMER BACKBONE			
)	)	)	)
(	(	(	(
$NHSO_3^-$	SO_3^-	$[CH_2-CHR_1-O]_n-CH_3$	Hep

iv)

POLYMER BACKBONE			
)	)	)	)
(	(	(	(
$NHSO_3^-$	SO_4^-	SO_3^-	Hep

b) penta-polymer

POLYMER BACKBONE				
)	)	)	)	)
(	(	(	(	(
$NHSO_3^-$	SO_3^-	SO_4^-	$[CH_2-CHR_1-O]_n-CH_3$	Hep

These non-thrombogenic/anti-thrombogenic (NON-TH/ANTI-TH) polymers are of the kind represented above as Type 2.

Polymerisation may be carried out by conventional aqueous solution polymerisation using a water soluble initiator, such as potassium persulphate, after degassing the solution and under an inert gas, such as nitrogen. Reaction temperature for polymerisation is at room or elevated temperature, provided that the heparin biological activity is not affected. The preferred polymerisation temperature is one between 15 to 90°C, and generally a polymerisation temperature of 75°C is suitable. The polymer may be purified by conventional means, such as precipitation, filtration wash and dialysis.

The aforementioned non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer according to the invention is capable of being applied as a coating on medical devices for use in blood-contacting applications. In this regard, another aspect of this invention is the modification of polyethylene imine or other primary or secondary amino containing polymers to an extent that they form a stable attachment between the medical device and the non-thrombogenic polymer or the non-thrombogenic/ anti-thrombogenic polymer.

The use of unmodified polyethylene imine as an anchoring point for heparin is known, EP 0124676. In these processes the medical device requires chemical pre-treatment to allow attachment of polyethylene imine to occur. Additionally, multi-layers are built up on the device to ensure good coverage and to enhance the stability of the attachment. These are disadvantages which have severe impact on the performance and the coating process. The heparin attached is grafted onto the external polyethylene imine layer where surface covering is limited. There is predominately preferential ionic bonding of the heparin to the polyethylene imine. In such instances the heparin may be released from the surface. This coating

requires repeated steps to ensure that the polyethylene imine is bound effectively. This has the constraint of increasing the complexity of the process which results in high costs being incurred.

To overcome the disadvantages mentioned above we have devised a method for modifying primary or secondary amine polymers including polyethylene imine which can be attached to the medical device without any pre-treatment and can be carried out in a single step. This is achieved by increasing the molecular weight of the amine polymer, but to a limited extent, whereby the polymer does not gel, but remains in solution. This can, for instance, be achieved by crosslinking the amine, eg by treatment with a crosslinking agent, such as an alkylene diisocyanate, and/or with an alkyl isocyanate. The isocyanate crosslinking agents mentioned above react very quickly with the amino groups, but other crosslinking agents that are reactive with amino groups may be employed. These include, but are not limited to, diacids, diacid chlorides and cyclic anhydrides or dianhydrides. Generally there will be 4 to 16 carbon atoms between the active groups of the crosslinking agents. By increasing the hydrophobic nature of the amine polymer in this manner, it is capable of attaching to a suitable medical device sufficiently to allow attachment of the non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer. Hence the polymer coating process is essentially achieved in two steps, as opposed to multiple steps.

Attachment of the polymer to the polyethylene imine pre-coating can be enhanced by the incorporation of acrolein in the monomer feed for the non-thrombogenic/anti-thrombogenic polymer, giving aldehydic groups on the polymer backbone. These products are also novel. The aldehydic groups are allowed to react with amino groups on the modified polyethylene imine to form a Schiff's base which is reduced to form a stable covalent bond.

Alternatively the non-thrombogenic/anti-thrombogenic polymer may be attached to the modified polyethylene imine by ionic interaction.

The invention is illustrated by the following Examples, which are not intended to restrict the scope of the invention. In the Examples, concentrations are expressed as percentages weight/volume, i.e. grams weight per 100ml of solution.

The structure of the polymers whose preparation is identified in the following Examples can be confirmed by the presence of certain peaks in their FTIR spectra. These peaks include:

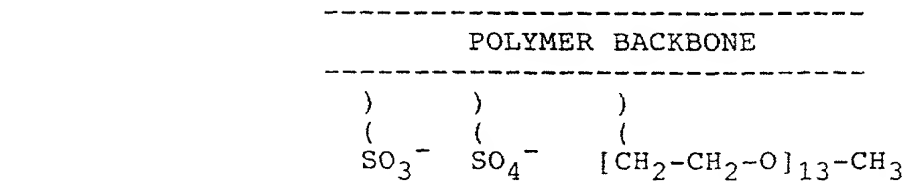
carbonate	1745.7 cm^{-1}
methacrylate	870 cm^{-1} and 970 cm^{-1}
carboxylic acid (sodium salt or ester)	1609.8 cm^{-1}
carbohydrate hydroxyl	3500 cm^{-1}
C-O-C link in ester	1250 cm^{-1}

EXAMPLES 1 TO 5: THE FORMATION OF NON-THROMBOGENIC POLYMERS

Example 1

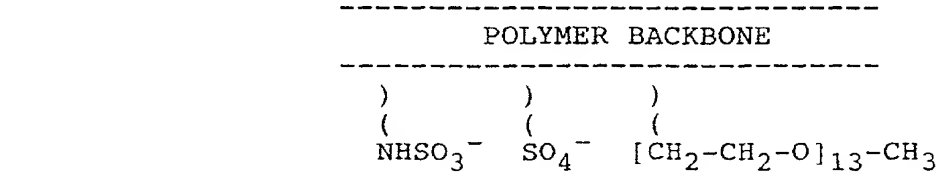
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 9.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 45g) and vinyl sulphonic acid sodium salt (25% aqueous solution, 13g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the

contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



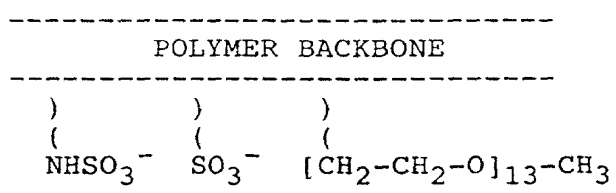
Example 2

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 7.7g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 40.8g) and 2-sulphamatoethyl methacrylamide (25% aqueous solution, 22.4g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 3

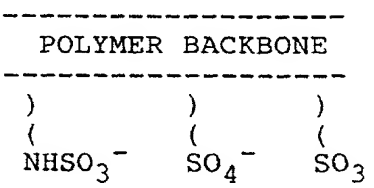
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 8.6g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 45.2g) and vinyl sulphonic acid sodium salt (25% aqueous solution, 14.4g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 4

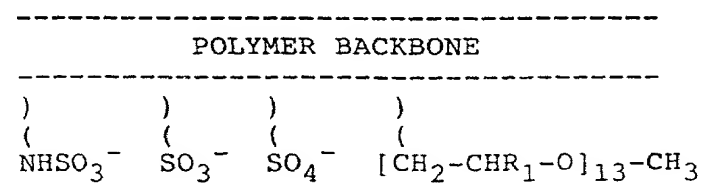
2-Sulphamatoethyl methacrylamide (25% aqueous solution, 16.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 59.6g) and vinyl sulphonic acid sodium salt (25% aqueous solution, 18.4g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of

the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 5

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13. 9.3g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 17.6g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 26.4g) and vinyl sulphonic acid sodium salt (25% aqueous solution, 12.8g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



EXAMPLE 6: THE FORMATION OF ACTIVATED IMIDAZOYL CARBONATE

Hydroxy polyethyleneglycol methacrylate (PEG, n=7, 1.0g) was added drop-wise to carbonyldiimidazole (Im-C(=O)-Im; 0.5g) in anhydrous dichloromethane to form the activated imidazoyl carbonate:

$CH_2=C(CH_3)-C(=O)-O-CH_2-CH_2-[O-CH_2-CH_2-]_7-O-C(=O)-Im$

The solution was stirred for 3 hours for the reaction to be completed and dichloromethane was removed on a rotary evaporator.

EXAMPLE 7: FORMATION OF HEPARIN MONOMER

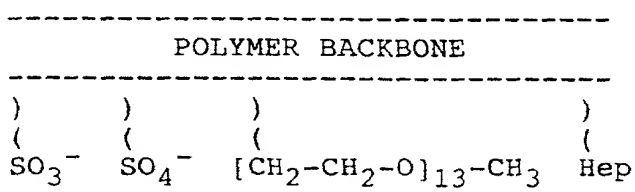
Heparin (injectable grade, 5.0g) was dissolved in 30ml of water. The heparin solution was then added to the activated imidazoyl carbonate formed in Example 6. The pH of the solution was adjusted to 8.5 to 9.0 by using potassium bicarbonate and and solution was stirred for 24 hours to form the heparin monomer. The solution was then adjusted to pH7 with HCl.

EXAMPLES 8 TO 12: THE FORMATION OF NON-THROMBOGENIC/ANTI-THROMBOGENIC POLYMERS

Example 8

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 9.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 45g), vinyl sulphonic acid (25% aqueous solution, 13g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were

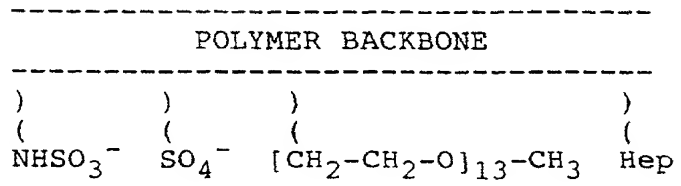
degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 9

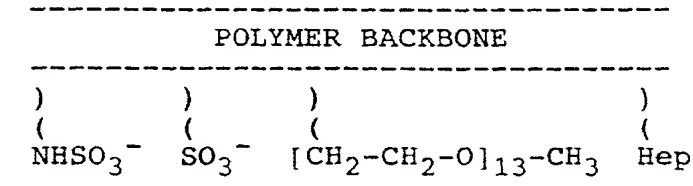
Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 7.7g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 40.8g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 22.4g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000.

The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 10

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13. = 8.6g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 45.2g), vinyl sulphonic acid sodium salt (25% aqueous solution, 14.4g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:



Example 11

2-Sulphamatoethyl methacrylamide (25% aqueous solution, 16.0g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 59.6g), vinyl sulphonic acid sodium salt (25% aqueous solution, 18.4g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

POLYMER BACKBONE			
)	)	)	)
(	(	(	(
$NHSO_3^-$	SO_4^-	SO_3	Hep

Example 12

Methoxy polyethyleneglycol methacrylate (MPEG METH., n=13, 9.3g), 2-sulphamatoethyl methacrylamide (25% aqueous solution, 17.6g), ammonium sulphatoethyl methacrylate (25% aqueous solution, 26.4g), vinyl sulphonic acid sodium salt (25% aqueous solution, 12.8g) and the heparin monomer formed in Example 7 (5g) were added to a 250ml conical flask. The contents of the flask were degassed for 30 minutes, followed by bubbling with nitrogen and then heating to 75°C. Potassium persulphate (100mg) was dissolved in water (15ml) and added to the flask to

start polymerisation. The reaction was allowed to continue for 15 minutes after which a very viscous solution was obtained. The reaction was stopped by pouring the contents of the flask into a beaker containing cold water (100ml). The resultant polymer was dialysed against 10 litres of water in cellulose acetate membrane, M.W. cut off at 12,000 to 14,000. The polymer was removed and concentrated to 150ml and stored at 5°C. The anionic portion of the polymer composition can be illustrated as follows:

POLYMER BACKBONE				
)	)	)	)	)
(	(	(	(	(
$NHSO_3^-$	SO_3^-	SO_4^-	$[CH_2\text{-}CHR_1\text{-}O]_{13}\text{-}CH_3$	Hep

EXAMPLES 13 AND 14: MODIFICATION OF POLYETHYLENE IMINE (PEI)

PEI was supplied as a 50% solution in water by BASF, approximate molecular weight is 20,000.

Example 13

PEI (140g) was dissolved in 1 litre of isopropanol. Hexamethylene diisocyanate (2.8g) was dissolved in 50ml of acetone. The diisocyanate solution was added drop-wise to the PEI solution. The final solution was then rotary evaporated to remove the isopropanol (500ml).

Example 14

PEI (140g) was dissolved in 500ml of isopropanol. Hexamethylene diisocyanate (1.4g) was dissolved in 50ml of

acetone. The diisocyanate solution was added drop-wise to the PEI solution. A solution of n-butyl isocyanate (2.0g in 50ml acetone) was then added drop-wise to the solution.

EXAMPLES 15 AND 16: FORMATION OF SOLUTION FOR COATING

Five mole percent of acrolein is added to the monomer feed in the formation of the non-thrombogenic polymer or the non-thrombogenic/anti-thrombogenic polymer. This allows chemical linkage to the modified polyethylene imine.

Example 15

The modified polyethylene imine as prepared in Example 13 is diluted to give a final composition of 0.23%. The pH of the solution is in the region of 9.5 to 10. Samples of medical devices, generally tubing, connectors and the like are coated by incubating in the solution for 10 minutes, and then washed with distilled water. Typically, the tubing may by polyvinyl chloride, polyethylene or silicone, and the connectors polycarbonate or polyvinyl chloride.

Example 16

The non-thrombogenic polymer or the non-thrombogenic/ anti-thrombogenic polymer is prepared as in the aforementioned Examples and is diluted with water to give a final polymer concentration of 0.08% (w/v). The pH of the solution is adjusted to 8.5 with sodium tetraborate. After the samples have been incubated in the modified polyethylene imine, as described in Example 15, the samples are incubated in the

non-thrombogenic polymer or the non-thrombogenic/ anti-thrombogenic polymer for 10 minutes. The samples are then washed and tested for haemocompatibility.

The polymer from Example 1 (non-thrombogenic polymer) and Example 8 (non-thrombogenic/anti-thrombogenic polymer) were assessed for haemocompatibility. The results showed that in both types of polymers, Example 1 (non-thrombogenic polymer) and Example 8 (non-thrombogenic/anti-thrombogenic polymer), when coated on medical devices, the blood cell and protein deposition was reduced by greater than 90% and also greatly reduced (>95%) activation of white cells, platelets and complement activation. Medical devices coated with the product of Example 8 (non-thrombogenic/anti-thrombogenic polymer) showed the additional property of reducing the thrombin-antithrombin complex concentration.

CLAIMS

1. Polymers comprising a polymer backbone having pendant groups, obtainable by polymerizing monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

(a) monomers having sulphate groups
(b) monomers having sulphonate groups
(c) monomers having sulphamate groups, and
(d) monomers having polyoxyalkylene ether groups

2. Polymers comprising a polymer backbone having pendant groups, obtainable by polymerizing monomers having such groups, characterized in that said polymers are obtained by copolymerizing monomers of at least three different classes selected from:

(a) monomers having sulphate groups
(b) monomers having sulphonate groups
(c) monomers having sulphamate groups, and
(d) monomers having polyoxyalkylene ether groups
(e) monomers having zwitterionic groups

3. Polymers according to Claim 1 or 2 characterized in that said monomers in Classes (a), (b) and/or (c) have the formula

$$CH_2=CR_1\text{-}C(=O)\text{-}Z_1\text{-}R_2\text{-}Y_1\text{-}X_1$$

where

R_1 is H or CH_3;

R_2 is a linear or branched alkylene of 2-10 carbon atoms, phenylene, phenyl alkylene with 1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure $[CH_2\text{-}CHR_1\text{-}O]_n$ where R_1 is H or CH_3 and n is from 2 to 50;

Z_1 is oxygen (-O-) to give an ester linkage or secondary amine (-NH-) to give an amide linkage;

Y_1 is (-O-) or (-NH-) or is absent; and

X_1 is sulphonate ($-SO_3^-$).

together with an acceptable balancing cation.

4. Polymers according to Claim 1 or 2 characterized in that said monomers in Classes (a), (b) and/or (c) have the formula:

$$CH_2=CR_1\text{-}R_2\text{-}Y_1\text{-}X_1$$

where

R_1 is H or CH_3;

R_2 is a linear or branched alkylene of 1-10 carbon atoms, phenylene, phenyl alkylene with 1-10 carbon atoms in the alkylene structure or the polyoxyalkylene structure $[CH_2\text{-}CHR_1\text{-}O]_n$ where R_1 is H or CH_3 and n is from 2 to 50;

Y_1 is (-O-) or (-NH-) or is absent; and

X_1 is sulphonate ($-SO_3^-$).

together with an acceptable balancing cation.

5. Polymers according to any one of Claims 1 to 4 characterized in that the monomer containing sulphate groups is selected from salts of 2-sulphatoethyl methacrylate, 2-sulphatoethyl acrylate, 3-sulphatopropyl methacrylate, 3-sulphatopropyl acrylate, 4-sulphatobutyl methacrylate, 4-sulphatobutyl acrylate, allyl sulphate, methyl allyl sulphate, 3-buten-1-sulphate, 3-buten-2-sulphate, 2-methyl-2-propane-1-sulphate, 2-methyl-3-buten-1-sulphate, 3-methyl-3-buten-1-sulphate, 2-sulphatoethyl methacrylamide, 2-sulphatoethyl acrylamide, 3-sulphatopropyl methacrylamide, 3-sulphatopropyl acrylamide, 4-sulphatobutyl methacrylamide, 4-sulphatobutyl acrylamide, sulphato polyoxyalkylene methacrylate, and sulphato polyoxyalkylene acrylate.

6. Polymers according to any one of Claims 1 to 5 characterized in that the monomer containing sulphonate groups is selected from salts of 2-sulphoethyl methacrylate, 2-sulphoethyl acrylate, 3-sulphopropyl methacrylate, 3-sulphopropyl acrylate, vinyl sulphonate, allyl sulphonate, methyl allyl sulphonate, p-styrene sulphonate, 2-acrylamide-methylpropanesulphonate, 3-sulphopropyl ethoxy methacrylate, 3-sulphopropyl ethoxy acrylate, 3-sulphopropyl polyoxyalkylene methacrylate, and 3-sulphopropyl polyoxyalkylene acrylate.

7. Polymers according to any one of Claims 1 to 6 characterized in that the monomer containing sulphamate groups is selected from salts of 2-

sulphamatoethyl methacrylate, 2-sulphamatoethyl acrylate, 3-sulphamatopropyl methacrylate, 3-sulphamatopropyl acrylate, 4-sulphamatobutyl methacrylate, 4-sulphamatobutyl acrylate, allyl sulphamate, methyl allyl sulphamate, 2-sulphamatoethyl methacrylamide, 2-sulphamatoethyl acrylamide, 3-sulphamatopropyl methacrylamide, 3-sulphamatopropyl acrylamide, 4-sulphamatobutyl methacrylamide, 4-sulphamatobutyl acrylamide, sulphamato polyoxyalkylene methacrylate and sulphamato polyoxyalkylene acrylate.

8. Polymers according to any one of Claims 1 to 6 characterized in that said monomers in Class (d) have the formula

$$CH_2=CR_3-C(=O)-O-[CH_2-CHR_4-O]_n-R_7$$

where R_3 and R_4, which may be the same or different, are each H or CH_3; R_7 is H or alkyl with from 1 to 5 carbon atoms; and n is from 2 to 50.

9. Polymers according to any one of Claims 1 to 8 characterized in that said polymers comprise heparin monomer units having heparin, linked to a polymerizable moiety having a carbon-carbon double bond.

10. Polymers according to any one of Claims 1 to 8 characterized in that said polymers comprise monomer units having hirudin, warfarin or hyaluronic acid linked to a polymerizable moiety having a carbon-carbon double bond.

11. Polymers according to Claim 9 characterized in that the heparin monomer units comprise vinyl, allyl, methallyl, acrylate or methacrylate groups.

12. Polymers according to Claim 9 or 11 characterized in that the heparin monomer has the formula:

$$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-Heparin$$

or

$$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-O-Heparin$$

where R_5 and R_6, which may be the same or different, are each H or CH_3; and n is from 0 to 49.

13. Polymers according to any one of Claims 1 to 12 characterized in that said polymers contain additional monomer units derived from acrolein.

14. A medical device having a coating of a polymer according to any one of Claims 1 to 13.

15. A method of forming a coating of a polymer according to any one of Claims 1 to 14 on a medical device, characterized by forming an ungelled partial polymer by reacting a solution of an amine polymer with a crosslinking agent, activating the medical device by solution coating with said partial polymer, and depositing the polymer on the resulting activated medical device.

16. A method according to Claim 15 characterized in that the amine polymer is polyethylene imine.

17. A method according to any one of claims 15 and 16 characterized in that the crosslinking agent is an aliphatic monoisocyanate or diisocyanate.

18. A heparin monomer having the formula:

$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-Heparin$

or

$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-O-C(=O)-O-Heparin$

where R_5, R_6 and n have the meanings given in Claim 12.

19. A method of forming a heparin monomer according to Claim 16, characterized in that a hydroxyl terminated compound of the formula:

$CH_2=CR_5-C(=O)-O-CH_2-CHR_6-[O-CH_2-CHR_6-]_n-OH$

is reacted with carbonyldiimidazole to form an activated imidazoyl carbonate of the formula:

$CH_2=CR_1-C(=O)-O-CH_2-CHR_2-[O-CH_2-CHR_2-]_n-O-C(=O)=Im$

wherein R_5, R_6 and n have the meanings given in Claim 18 and the activated imidazoyl carbonate is coupled with heparin at a basic pH.

20. A coating material comprising a polymer according to any one of claims 1 to 13.

21. A coating material according to Claim 20 characterized in that it is adapted for use on a surface of a medical device.

PATENT

Attorney's Docket No.

COMBINED DECLARATION AND POWER OF ATTORNEY

(Original, Design, National Stage of PCT or CIP Application)

Inventors: Ajay Kumar LUTHRA and Shivpal Singh SANDHU

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are stated below next to my name, I believe I am the original, first and sole inventor (if only one name is listed above) or an original, first and joint inventor along with those listed above (if plural names are listed above) of the subject matter which is claimed and for which a patent is sought on the invention entitled: Non-Thrombogenic and Anti-Thrombogenic Polymers

the specification of which: (Complete (a), (b) or (c) for type of application)

REGULAR OR DESIGN APPLICATION

(a) __ is attached hereto.

(b) ___ was filed on _____ as Application Serial No.
and was amended on _____ (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

(c) _X_ was described and claimed in International Application No PCT/GB97/01173
filed on 30 April 1997 and as amended on (if any)

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

___ In compliance with this duty there is attached an information disclosure statement.
37 CFR 1.97.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

[Complete (d) or (e)]

(d) ___ no such applications have been filed.

(e) _x_ such applications have been filed as follows.

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION

Country	Application No.	Date of filing (day, month, year)	Date of issue (day, month, year)	Priority Claimed
Great Britain	9608882.8	30 April 1996		_x_ YES NO ___
				___ YES NO ___

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION

CONTINUATION-IN-PART

(Complete this part only if this is a continuation-in-part application)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing Date)	(Status)	(Patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status)	(Patented, pending, abandoned)

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney and/or agent to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith, before all competent international authorities in connection with any international application, and before all foreign patent offices in connection with the national phase of any international application or any foreign application, and to appoint any associate attorneys in connection with any application, either domestic, international or foreign national.

John M. Howell (25,261); Richard E. Haferkamp (29,072); Kenneth Solomon (31,427); Joseph M. Rolnicki (32,653); Joseph E. Walsh, Jr. (36,959); Alan H. Norman (32,285); Donald R. Holland (35,197); Bryan K. Wheelock (31,441); Charles E. Dunlap (35,124); Anthony G. Simon (40,813); Alan L. Cassel (35,842); Michael J. Thomas (39,857); Thomas A. Polcyn (41,256); Melodie W. Henderson (37,848); and Michael E. Kondoudis (P42,758)

Send Correspondence To
Charles E. Dunlap
HOWELL & HAFERKAMP, L.C.
7733 Forsyth Boulevard
Suite 1400
St. Louis, Missouri 63105

Direct Telephone Calls To

Charles E. Dunlap
(314) 727-5188

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor LUTHRA, Ajay Kumar

Inventor's signature A Luthra

Date 21st October 1998 Country of Citizenship Great Britain

Residence Middlesex, England

Post Office Address 219 Somervell Road, South Harrow, Middlesex HA2 8UA England

Full name of second inventor SANDHU, Shivpal Singh

Inventor's signature S S Sandhu

Date 21 OCTOBER 1998 Country of Citizenship Great Britain

Residence Berkshire, England

Post Office Address 63 Lascelles Road, Slough, Berkshire SL3 7PW England